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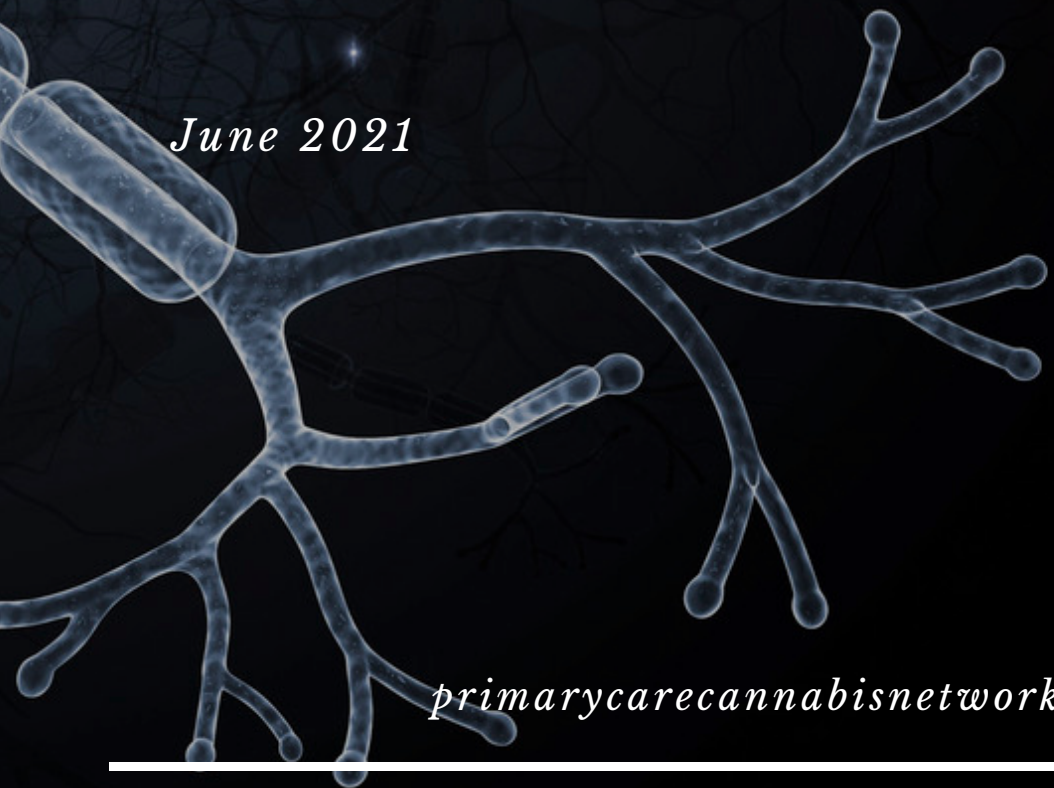
THE ENDOCANNABINOID SYSTEM

A summary reference guide to the main components mechanism and function of the endocannabinoid system.

June 2021



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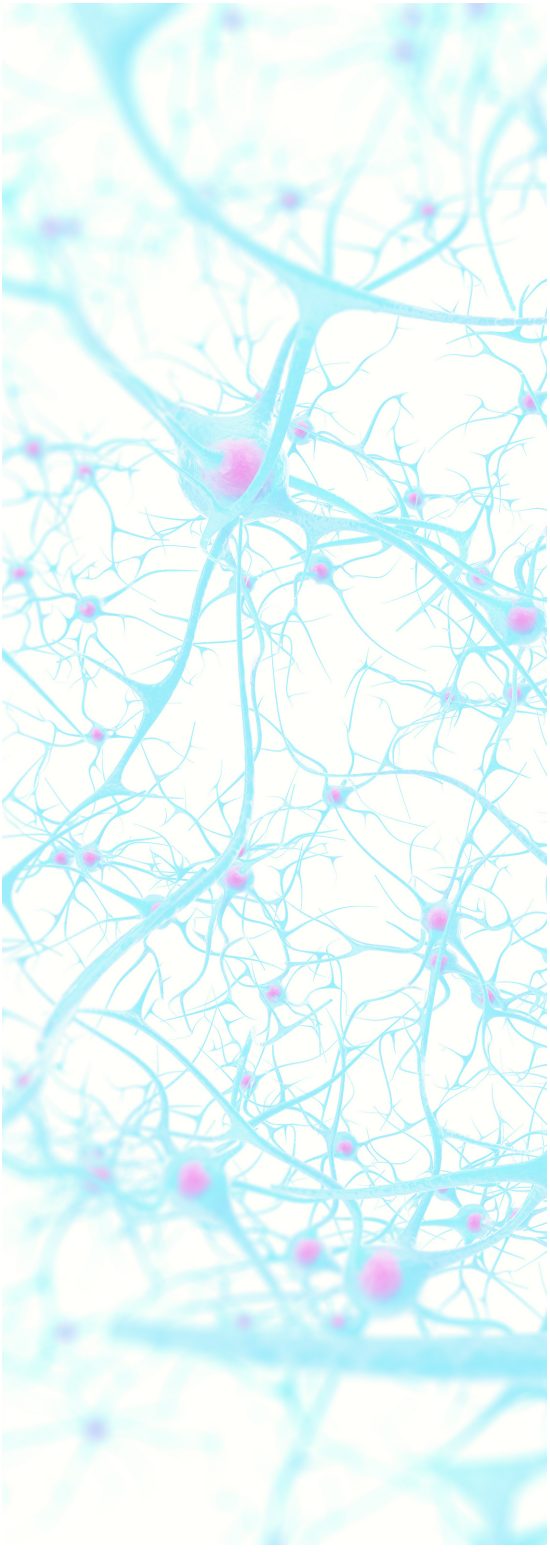
CONTENTS



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THE ENDOCANNABINOID SYSTEM

The Endocannabinoid System (ECS) is complex biological system of receptors and neurotransmitters that was first discovered in the 1980s and 1990s. The ECS is present in central and peripheral nervous systems and in peripheral organs and plays a critical role in a wide range of physiological processes and in maintaining homeostasis. The ECS is universal to all vertebrates and is implicated in vast array of physiological functions and disease states that include:

- Anxiety
- Appetite
- Autonomic functions
- Bladder function
- Cancer control
- Energy balance
- Female reproductive function
- GI function
- Homeostasis
- Inflammation
- Memory
- Metabolic functions
- Cell growth and proliferation
- Motor control
- Neurogenesis
- Neuroprotection
- Neuroplasticity
- Neurotransmission
- Regulation of pain
- Sleep
- Stress response
- Thermoregulation

The three components of the Endocannabinoid System are:

- Cannabinoid receptors
- Endocannabinoids
- Enzymes that regulate the formation and breakdown of endocannabinoids.

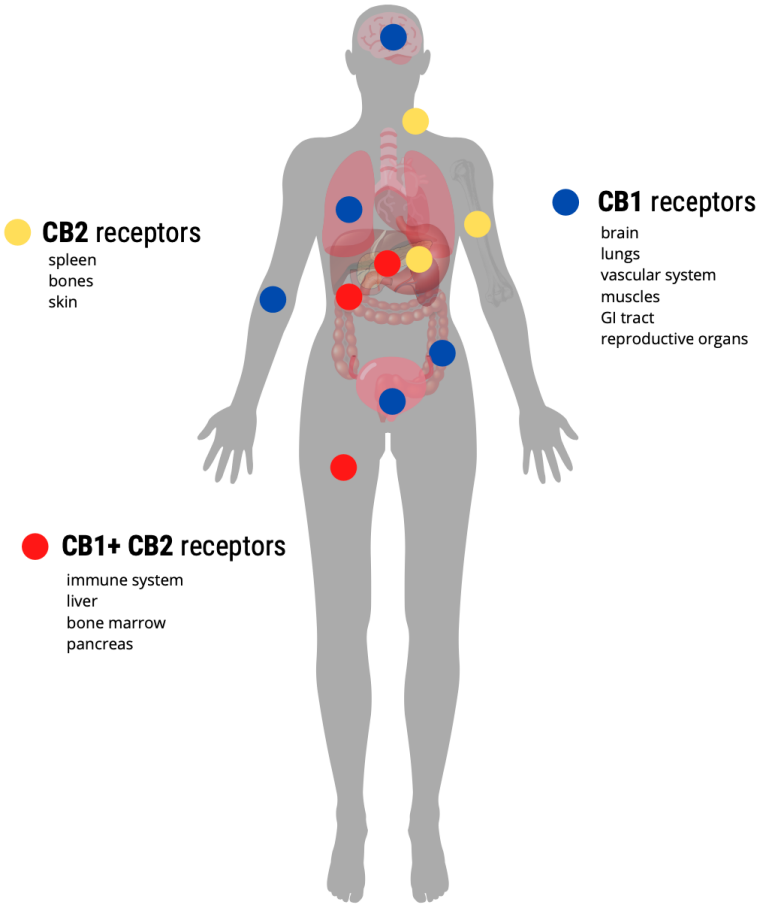
CANNABINOID RECEPTORS

The endocannabinoid system is the most widespread receptor system in humans and regulates many of our most important physiological functions.

CB1 and CB2 are cannabinoid receptors found on presynaptic neurons that detect molecules outside the cell to mediate most of our physiological responses to hormones, neurotransmitters and environmental stimulants. Cannabinoid receptors are of a class of cell membrane receptors in the G protein-coupled receptor family

CB1 receptors are predominately found at the presynaptic terminals in the central nervous system and in the peripheral nervous system, heart and gastrointestinal tract .

CB2 receptors are more abundant in the immune system and in the peripheries [1-2].



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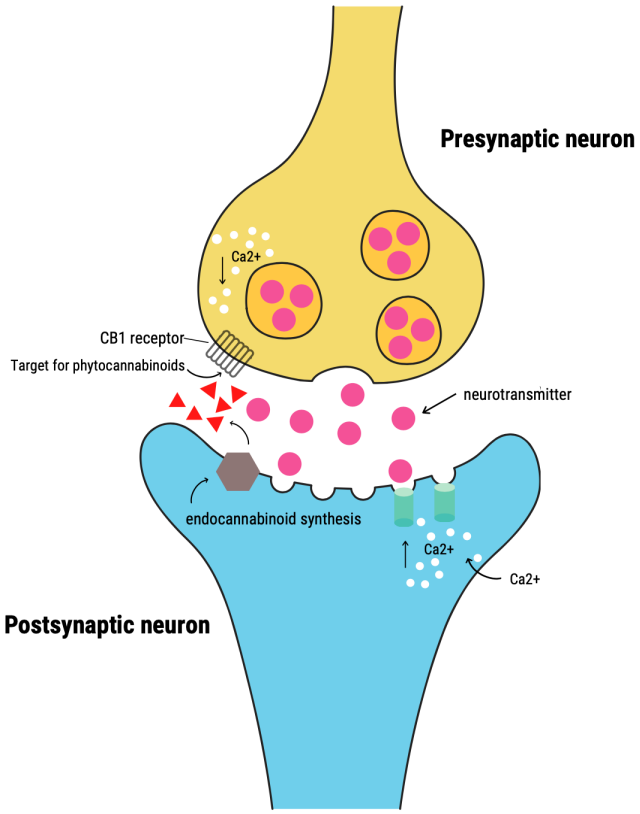
ENDOCANNABINOIDS

Endocannabinoids are naturally produced neuromodulators (ligands) that bind and activate to cannabinoid receptors. Our two major endocannabinoids are Anandamide and 2-AG and are synthesised on demand. Endocannabinoids are found in all tissues, organs and bodily fluids and are released by post-synaptic neurons, and bind to the presynaptic CB1 and CB2 receptors to moderate the release of neurotransmitters including GABA, glutamate, and dopamine [1-2].



Retrograde signalling (where a signal travels backwards from a target source to its original source) permits endocannabinoids to regulate signalling activity across a wide range of physiological functions and substrate specific enzymes are involved in biosynthesis and degradation of endocannabinoids [1-2].

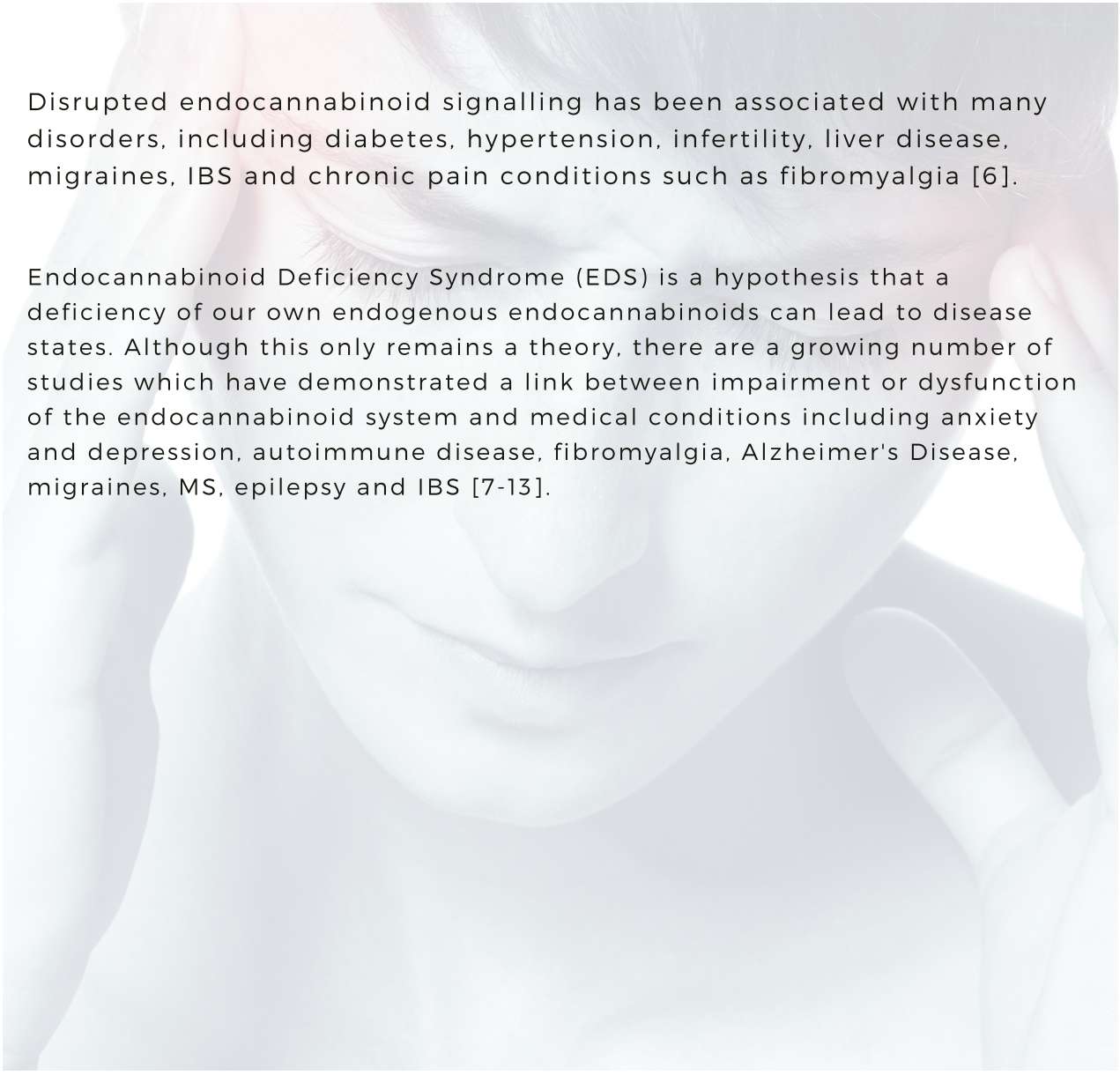
Endocannabinoids also work at various target sites in the brain and peripheries including:

- GPR55 or G protein-coupled receptor 55 which pain and production of endocannabinoids [3].

- PPARs or peroximsome proliferator-activated receptors which regulate the translation of genes involved in metabolism and energy homeostasis [4].

- TRPV or transient receptor vanilloid, a family of protein ion channels that are involved in inflammation and pain response [5].

DISEASE STATES



Disrupted endocannabinoid signalling has been associated with many disorders, including diabetes, hypertension, infertility, liver disease, migraines, IBS and chronic pain conditions such as fibromyalgia [6].

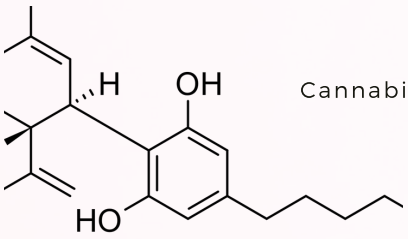
Endocannabinoid Deficiency Syndrome (EDS) is a hypothesis that a deficiency of our own endogenous endocannabinoids can lead to disease states. Although this only remains a theory, there are a growing number of studies which have demonstrated a link between impairment or dysfunction of the endocannabinoid system and medical conditions including anxiety and depression, autoimmune disease, fibromyalgia, Alzheimer's Disease, migraines, MS, epilepsy and IBS [7-13].

PHYTOCANNABINOIDS

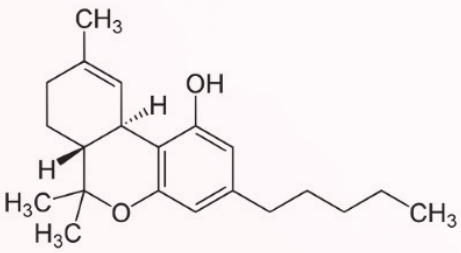
The cannabis plant *Cannabis sativa* produces many active compounds including phytocannabinoids which have molecular similarities to our own endocannabinoids and are able to directly interact with and modulate our own endogenous endocannabinoid system [14-15].

Phytocannabinoids are synthesised and concentrated in the upper leaves of the unfertilised female cannabis flower and made as a resin by glandular trichomes. To date there are around 120 known phytocannabinoids in the cannabis plant [16]. The most commonly known and widely studied phytocaannabinoids are Cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC). New phytocannabinoids continue to be discovered (recent examples include CBG, THCV and CBN) and clinical trials that set out to deepen our understanding of the pharmacological activity of these are now gathering pace across the globe.

Synthetically produced cannabinoids such Nabilone (which mimics THC and is licenced for use in chemotherapy induced nausea and vomiting) are also able to activate cananbinoid receptors.



Cannabidiol



Delta-9-tetrahydrocannabinol

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